



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,262	03/26/2004	Stuart Naylor	674523-2029.1	1123
20999	7590	06/27/2006	EXAMINER	
FROMMER LAWRENCE & HAUG 745 FIFTH AVENUE- 10TH FL. NEW YORK, NY 10151			CHEN, SHIN LIN	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 06/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/810,262

Applicant(s)

NAYLOR ET AL.

Examiner

Shin-Lin Chen

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-46 is/are pending in the application.
- 4a) Of the above claim(s) 19-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-18 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 26 March 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☒ Certified copies of the priority documents have been received in Application No. 09/787,562.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>3-26-04</u> . | 6) <input type="checkbox"/> Other: _____  |

### DETAILED ACTION

1. Applicant's election of group I, claims 1-18, in the reply filed on 5-11-06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 19-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Election was made **without** traverse in the reply filed on 5-11-06.

Applicants' preliminary amendment filed 7-21-04 has been entered. Claims 1-46 are pending. Claims 1-18 are under consideration.

### *Priority*

The parent applications 09/787,562, PCT/GB99/03181, PCTGB98/02885, United Kingdom 9901906.9 and 9903538.8 fail to disclose the subject matter of the instant invention, i.e. a method for treating ocular neovascularization by delivering to the target cells in the eye of a subject a vector expressing an angiostatic gene product under the control of a promoter. Therefore, the priority dates of those parent applications are not granted. Thus, the priority of the instant invention is the filing date of the present application, 3-26-04.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

Art Unit: 1632

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting retinal or choroidal neovascularization by direct injection of a viral vector expressing pigment epithelium-derived factor (PEDF), angiostatin, or VEGF/flt-1 receptor to target eye cells as discussed in the references below under 35 U.S.C. 102 and 103 rejections, does not reasonably provide enablement for a method of treating ocular neovascularization by delivering to the target cells in the eye of a subject a vector expressing any angiostatic gene product under the control of any promoter via various administration routes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1-18 are directed to a method for treating ocular neovascularization comprising delivering to target cells in the eye of a subject a vector comprising a promoter, such as a physiologically regulated promoter (e.g. hypoxic response element) or a constitutive promoter (e.g. CVM promoter) operably linked to a polynucleotide sequence encoding an angiostatic gene product, such as endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and PEDF. Claim 6 specifies the ocular neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claim 7 specifies the ocular neovascularization is choroidal or retinal neovascularization. Claims 8-11 specify the vector is a viral vector, such as retroviral vector, such as lentiviral vector, or adeno-associated viral vector. Claims 12 and 13 specify the target cells are retinal cells, such as retinal pigment epithelial cells. Claim 14 specifies the delivery is

Art Unit: 1632

via direct sub-retinal injection. Claims 16-18 specify the vector further comprises a polynucleotide sequence encoding at least one additional angiostatic gene product.

The specification discloses preparation of EIAV-OBHRE recombinant LentiVector and shows hypoxially regulated LacZ expression in transduced human retinal pigment epithelial cells *in vitro*, (example 2), and subretinal injection of LentiVector shows OBHRE mediated LacZ expression in localized regions of the laser treated retina (example 3). The claims encompass treating ocular neovascularization by delivering a vector expressing an angiostatic gene product under any promoter to the target cells in the eye of a subject via various administration routes. The specification fails to provide adequate guidance and evidence for how to administer a vector expressing any angiostatic gene product under any promoter to the target cells in the eye of a subject via various administration routes such that sufficient angiostatic gene product can be obtained at the target cells in the eye so as to provide therapeutic effect *in vivo* for treating ocular neovascularization, e.g. retinal or choroidal neovascularization.

The claims read on gene transfer and gene therapy *in vivo*. The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the

Art Unit: 1632

art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Whether sufficient gene product can be obtained at the target cells in the eye depends on the type of promoter used and the activity of said promoter in said target cells. Some promoters have no gene expression activity in the target cells in the eye. Verma states that “The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses.” (e.g. p. 239, column 3).

Administration route and the process of how the transgene reach its target cells and the expression of said transgene play important role in whether sufficient transgene product can be obtained at the target site in vivo so as to provide therapeutic effect in a subject. Eck et al., 1996 (Goodman & Gilman’s The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the

Art Unit: 1632

protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In addition, Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g. abstract).

The claims encompass using nucleotide sequences encoding various angiostatic gene products including andostatin, angiostatin, PEDF etc., and various unknown and unidentified angiostatic gene product, for treating ocular neovascularization in a subject. However, different angiostatic gene products have different amino acid sequences and their biological functions would differ. It was known in the art that the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Davis, C. G., 1990 (The New Biologist, Vol. 2, No. 5, p. 410-

Art Unit: 1632

419) reports that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid contexts, i.e. different proteins.

Further, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention and even same short stretch of amino acid sequence can show diverse biological functions while surrounded by different background amino acid sequences.

In view of the unpredictable nature of gene therapy in vivo, the limitation of using different viral vectors in gene delivery, and the unpredictable biological function of a protein from mere amino acid sequence, one skilled in the art at the time of the invention would not know how to use various vectors expressing various angiostatic gene products under the control of a promoter for treating ocular neovascularization in a subject via various administration routes so as to provide therapeutic effect in vivo. One of skilled in the art would require to identify and

Art Unit: 1632

characterize the nucleotide sequence of the unknown and unidentified angiostatic gene products, trial and error experimentation to determine the biological function of various angiostatic gene products, preparation of various vectors, including viral vectors, expressing various angiostatic gene products, trial and error experimentation to determine how to administer said vector to a subject via various administration routes such that sufficient angiostatic gene products can be obtained at the target cells in the eye in a subject, and trial and error experimentation to determine whether the expressed angiostatic gene products can provide therapeutic effects for treating ocular neovascularization in said subject in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Art Unit: 1632

6. Claims 1, 2, 5-8 and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Honda et al., 2000 (Gene Therapy, Vol. 7, p. 978-985).

Claims 1, 2, 5-8 and 12-15 are directed to a method for treating ocular neovascularization comprising delivering to target cells in the eye of a subject a vector comprising a promoter, such as a constitutive promoter (e.g. CVM promoter) operably linked to a polynucleotide sequence encoding an angiostatic gene product, such as endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and PEDF. Claim 6 specifies the ocular neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claim 7 specifies the ocular neovascularization is choroidal or retinal neovascularization. Claim 8 specifies the vector is a viral vector. Claims 12 and 13 specify the target cells are retinal cells, such as retinal pigment epithelial cells. Claim 14 specifies the delivery is via direct sub-retinal injection.

Honda teaches preparation of an adenovirus expressing an entire ectodomain of the human VEGF receptor/flt-1 fused to Fc portion of human IgG (Adfit-ExR), injection of Adfit-ExR into the femoral muscle, and shows the expressed VEGF soluble receptor significantly inhibit subretinal neovascularization (SRN) (e.g. abstract). Thus, claims 1, 2, 5-8 and 12-15 are anticipated by Honda.

7. Claims 1, 2, 5-8 and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Gehlbach et al., 2002 (ARVO Annual Meeting Abstract Search and Program Planner, Vol. 2002, Abstract No. 4595).

Art Unit: 1632

Claims 1, 2, 5-8 and 12-15 are directed to a method for treating ocular neovascularization comprising delivering to target cells in the eye of a subject a vector comprising a promoter, such as a constitutive promoter (e.g. CVM promoter) operably linked to a polynucleotide sequence encoding an angiostatic gene product, such as endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and PEDF. Claim 6 specifies the ocular neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claim 7 specifies the ocular neovascularization is choroidal or retinal neovascularization. Claim 8 specifies the vector is a viral vector. Claims 12 and 13 specify the target cells are retinal cells, such as retinal pigment epithelial cells. Claim 14 specifies the delivery is via direct sub-retinal injection.

Gehlbach teaches preparation of an adenoviral vector expressing PEGF under the control of a CMV promoter (AdPEDF.11), periocular injection of said adenoviral vector into the eye of mouse, and shows both systemic and local delivery of PEDF and inhibition of choroidal neovascularization (e.g. abstract). Thus, claims 1, 2, 5-8 and 12-15 are anticipated by Gehlbach.

8. Claims 1, 2, 6-8 and 12-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Takahashi et al., May 2003 (The FASEB Journal, Vol. 17, No. 8, pp. 896-898).

Claims 1, 2, 6-8 and 12-15 are directed to a method for treating ocular neovascularization comprising delivering to target cells in the eye of a subject a vector comprising a promoter, such as a physiologically regulated promoter, operably linked to a polynucleotide sequence encoding an angiostatic gene product, such as endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and PEDF. Claim 6 specifies the ocular neovascularization results

Art Unit: 1632

in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claim 7 specifies the ocular neovascularization is choroidal or retinal neovascularization. Claim 8 specifies the vector is a viral vector. Claims 12 and 13 specify the target cells are retinal cells, such as retinal pigment epithelial cells. Claim 14 specifies the delivery is via direct sub-retinal injection.

Takahashi teaches generation of a gutless adenoviral vector comprising tamoxifen-inducible expression of endostatin (InduceAGVendostatin) and subretinal injection of InduceAGVendostatin not only inhibits choroidal neovascularization but also retinal neovascularization in mice (e.g. p. 896, left column, p. 897). Thus, claims 1, 2, 6-8 and 12-15 are anticipated by Takahashi.

9. Claims 1, 2, 6-10 and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Igarashi et al., 2003 (Gene Therapy, Vol. 10, p. 219-226).

Claims 1, 2, 6-10 and 12-15 are directed to a method for treating ocular neovascularization comprising delivering to target cells in the eye of a subject a vector comprising a promoter operably linked to a polynucleotide sequence encoding an angiostatic gene product, such as endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and PEDF. Claim 6 specifies the ocular neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claim 7 specifies the ocular neovascularization is choroidal or retinal neovascularization. Claims 8-10 specify the vector is a viral vector, such as retroviral vector, such as lentiviral vector, or adeno-associated viral vector. Claims 12 and 13 specify the target

Art Unit: 1632

cells are retinal cells, such as retinal pigment epithelial cells. Claim 14 specifies the delivery is via direct sub-retinal injection.

Igarashi teaches generation of a HIV vector encoding angiostatin (HIV-angiostatin) under the control of a CAG promoter and intravitreal injection of HIV-angiostatin led to stable expression of the angiostatin in the retinal tissue and inhibition of retinal neovascularization in a murine proliferative retinopathy model (e.g. abstract), p. 220, left column). HIV vector is a lentiviral vector. Thus, claims 1, 2, 6-10 and 12-15 are anticipated by Igarashi.

10. Claims 1, 2, 5-8 and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Mori et al., 2001 (Journal of Cellular Physiology, Vol. 188, p. 253-263).

Claims 1, 2, 5-8 and 12-15 are directed to a method for treating ocular neovascularization comprising delivering to target cells in the eye of a subject a vector comprising a promoter, such as a constitutive promoter (e.g. CVM promoter) operably linked to a polynucleotide sequence encoding an angiostatic gene product, such as endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and PEDF. Claim 6 specifies the ocular neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claim 7 specifies the ocular neovascularization is choroidal or retinal neovascularization. Claim 8 specifies the vector is a viral vector. Claims 12 and 13 specify the target cells are retinal cells, such as retinal pigment epithelial cells. Claim 14 specifies the delivery is via direct sub-retinal injection.

Mori teaches preparation of an adenoviral vector encoding human PEDF under the control of a CMV promoter, and intravitreal injection of said adenoviral vector resulted in

Art Unit: 1632

expression of PEDF mRNA in the eye and inhibition of choroidal neovascularization and retinal vascularization in mice (e.g. abstract, p. 254, right column). Thus, claims 1, 2, 5-8 and 12-15 are anticipated by Mori.

11. Claims 1, 2, 6-10 and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Mori et al., 2002 (Investigative Ophthalmology & Visual Science, Vol. 43, No. 6, p. 1994-2000).

Claims 1, 2, 6-10 and 12-15 are directed to a method for treating ocular neovascularization comprising delivering to target cells in the eye of a subject a vector comprising a promoter operably linked to a polynucleotide sequence encoding an angiostatic gene product, such as endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and PEDF. Claim 6 specifies the ocular neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claim 7 specifies the ocular neovascularization is choroidal or retinal neovascularization. Claims 8-10 specify the vector is a viral vector, such as retroviral vector, such as lentiviral vector, or adeno-associated viral vector. Claims 12 and 13 specify the target cells are retinal cells, such as retinal pigment epithelial cells. Claim 14 specifies the delivery is via direct sub-retinal injection.

Mori teaches preparation of an adeno-associated viral vector (AAV-CBA-PEDF) expressing PEDF under the control of CMV enhancer and chicken-beta-actin promoter, and mice received intravitreal or subretina injection of said AAV-CBA-PEDF vector show significantly smaller area of choroidal neovascularization (CNV) as compared to control mice (e.g. p. 1995, left column, p. 1998, left column). Thus, claims 1, 2, 6-10 and 12-15 are anticipated by Mori.

Art Unit: 1632

12. Claims 1, 2 5-10 and 12-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Kovesdi et al., 2001 (WO 01/58494 A2).

Claims 1, 2, 5-10 and 12-15 are directed to a method for treating ocular neovascularization comprising delivering to target cells in the eye of a subject a vector comprising a promoter, such as a CMV promoter, operably linked to a polynucleotide sequence encoding an angiostatic gene product, such as endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and PEDF. Claim 6 specifies the ocular neovascularization results in proliferative diabetic retinopathy (PDR) or age-related macular degeneration (AMD) in the subject. Claim 7 specifies the ocular neovascularization is choroidal or retinal neovascularization. Claims 8-10 specify the vector is a viral vector, such as retroviral vector, such as lentiviral vector, or adeno-associated viral vector. Claims 12 and 13 specify the target cells are retinal cells, such as retinal pigment epithelial cells. Claim 14 specifies the delivery is via direct sub-retinal injection. Claims 16 and 17 specify the vector further comprises a polynucleotide sequence encoding at least one additional angiostatic gene product. Claim 18 specifies the angiostatic gene product is endostatin.

Kovesdi teaches a method of treating an animal for at least one ocular-related disorder, e.g. ocular neovascularization or age-related macular degeneration by contacting an ocular cell with an expression vector, such as an adenoviral vector, AAV vector, or a retrovirus vector (e.g. HIV vector), expressing an inhibitor of angiogenesis, such as PEDF, under the control of a promoter, such as a CMV promoter (e.g. abstract, [0019]-[0023], [0042]). The anti-angiogenic factors could be PEDF, angiostatin, endostatin and interferons etc. (e.g. [0053]). Kovesdi further teaches that the nucleic acid sequence encoding the inhibitor of angiogenesis encodes multiple

Art Unit: 1632

inhibitors of angiogenesis (claim 22), or the viral vector further comprises one or more additional nucleic acid sequence encoding therapeutic substance other than PEDF and said one or more additional nucleic acid sequence encodes an anti-angiogenesis substance (e.g. claims 36 and 39). Thus, claims 1, 2 5-10 and 12-18 are anticipated by Kovesdi.

***Claim Rejections - 35 USC § 103***

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al., May 2003 (The FASEB Journal, Vol. 17, No. 8, pp. 896-898) in view of Semkova et al., 2002 (ARVO Annual Meeting Abstract Search and Program Planner, Vol. 2002, pp. abstract No. 4616).

Claims 1 and 16-18 are directed to a method for treating ocular neovascularization comprising delivering to target cells in the eye of a subject a vector comprising a promoter operably linked to a polynucleotide sequence encoding an angiostatic gene product, such as endostatin, angiostatin, vascular endothelial growth factor receptor 1 (VEGFR1), FLT-1, and PEDF. Claims 16 and 17 specify the vector further comprises a polynucleotide sequence encoding at least one additional angiostatic gene product. Claim 18 specifies the angiostatic gene product is endostatin.

Takahashi teaches generation of a gutless adenoviral vector comprising tamoxifen-inducible expression of endostatin (InduceAGVendostatin) and subretinal injection of InduceAGVendostatin not only inhibits choroidal neovascularization but also retinal neovascularization in mice (e.g. p. 896, left column, p. 897).

Takahashi does not teach using a polynucleotide sequence encoding an additional angiostatic gene product for the treatment.

Semkova teaches subretinal injection of Hc-Ad.PEDF vector resulted in prominent immunohistochemical staining of transduced RPE cells and expressed PEDF released from the transduced cells inhibit pathological choroidal vascularization in rats. Semkova suggests that increased expression in RPE cell layer of PEDF and/or other therapeutic gene by Hc-Ad vector mediated gene transfer might provide a promising approach for the treatment of pathological ocular neovascularization.

It would have been obvious for one of ordinary skill in the art at the time of the invention to combine the use of polynucleotide sequences encoding endostatin and PEDF in a vector for the treatment of pathological ocular neovascularization because Takahashi teaches subretinal

Art Unit: 1632

injection of InduceAGVendostatin expressing endostatin not only inhibits choroidal neovascularization but also retinal neovascularization in mice and Semkova teaches using PEDF gene and other therapeutic gene in a Hc-Ad vector for the treatment of pathological ocular neovascularization.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to treat pathological ocular neovascularization as taught by Semkova with reasonable expectation of success.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of

Art Unit: 1632

the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

A handwritten signature in black ink, appearing to read 'S. Chen'.

**SHIN-LIN CHEN  
PRIMARY EXAMINER**